REMARKS

I. Status of Claims

Claims 1-39 were pending. Claims 6-11, 15-16, 18-19 and 27-35 have been canceled and new claims 40-53 added by this amendment. Claim 17 has been amended to relocate the colon. Claim 23 has been amended to correct the antecedent basis in the "wherein" clause of subpart (b). Claims 36-39 have been amended to eliminate their dependency from canceled claims. These amendments are therefore supported by the original claims. New claims 40-53 find support throughout the specification and original claims. In particular, claims 40-52 find support at least on page 17 and in Table 2 of the specification, in Examples 6 to 9, and in the original claims. Claim 53 finds support at least in the specification on pages 14-15, and 17, and in the original claims. This amendment adds no new matter.

Applicants note with appreciation that the Office has found Applicants' traversal of the September 22, 2004, Restriction Requirement partially convincing and rejoined and examined Groups I and II, claims 1-35. The Office has made final the restriction requirement for Group III, claims 36-39, and withdrawn these claims from further consideration. Claims 36-39 are process claims which depend from elected product claims. Applicants respectfully request that upon finding the product claims allowable, the Office rejoin and fully examine method claims 36-69, as required by rejoinder practice under M.P.E.P. § 821.04.

II. Rejection of claims 1-35 under 35 U.S.C. § 112-1, Scope of Enablement

The Office rejects claims 1-35 under 35 U.S.C. § 112, first paragraph, because according to the Office, the specification, while being enabling for the specific

constructs, "does not reasonably provide enablement for broad claims to a nucleic acid vector for the expression of at least two cistrons comprising any promoter, a variant fragment, homolog of SEQ ID NO. 1." Office Action, page 3. The Office addresses its reasons for alleging that the specification does not enable the full scope of the claims in several sections, which we also discuss individually.

A. Deposit Requirement

The Office first alleges that claims 1-35 lack enablement because the "invention consists of nucleic acid vectors . . . the host cells containing these vectors . . . and recombinant baculovirus." Office Action, page 4. The Office states that "[d]espite the fact that cloning DNA into vectors is well known in the art, there is no way of guaranteeing that a construct made by a skilled artisan will be exactly the same as the one used in the present invention." *Id.* The Office goes on to comment that there is "no way of guaranteeing that each stable Drosophila cell line or recombinant baculovirus taught in the specification will be exactly the same as that generated by another skilled artisan." *Id.* The Office concludes by noting that the "how to make" aspect of the enablement requirement may be satisfied by a deposit of the cell lines under the terms of the Budapest Treaty ("deposit requirement.") *Id.* at 5.

It is unclear why the Office has made a deposit requirement. Contrary to the Office's assertion, the claims do not require *exactly* the same vectors and host cells as described in the specification in order to practice the *claimed* invention. M.P.E.P. § 2164 states that "[t]he invention that one skilled in the art must be enabled to make and use is that defined by the claim(s) of the particular application or patent." The specific constructs and host cells disclosed in the specification provide working examples within

the scope of the claims, but the claims do not require these specific constructs. Because the claims do not recite a specific construct or host cell comprising a specific construct, a biological deposit is not required to enable the claims. The rejection of claims 1-35 based upon a deposit requirement should therefore be withdrawn.

B. "Promoter"

Claims 1-11, 17 and 18 are rejected under 35 U.S.C. § 112, first paragraph, because, according to the Office, the claims broadly encompass any promoter, but one skilled in the art "does not how to reliably isolate any length of genomic DNA and know that it would function as a promoter." Office Action, page 6. The Office Action lists the factors that must be considered in any determination that undue experimentation is required to practice the claimed invention. *Id.* (citing *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The Office points to Goswami et al., J. Mol. Evol. (2003) Vol. 57, pp. 44-51 ("*Goswami*"), to support the assertion that characterization of a promoter is a lengthy process. *Id.* The Office states that this characterization is undue experimentation, and argues that one of skill in the art "cannot define a regulatory region of a gene as a promoter and expect that another skilled in the art would select the same sequence without guidance." *Id* at 7. The Office disregards the remainder of the analysis under *In re Wands* in coming to its conclusion, however.

"A patent need not teach, and preferably omits, what is well known in the art." M.P.E.P § 2164.01 (citations omitted). The specification points out in the paragraph bridging pages 19 and 20 that promoters were well known in the art and that promoters in addition to those used in the working examples could be readily determined by those skilled in the art. At the time the invention was made, multiple companies offered

commercial vectors comprising promoters for use in various expression systems. The attached product description for Invitrogen Life Technologies' pcDNA3.1/His© A, B, and C vector provides one of many possible examples of a commercial expression vector comprising a promoter that was available prior to Applicants' filing date. This vector, like many other vectors, permits the insertion of genes of interest into a multiple cloning site: no manipulation or selection of the promoter is required. The state of the prior art with respect to the selection of promoters appropriate for use in various expression systems was therefore standardized and the level of skill in the art was very high.

In addition, *Goswami*, relied upon by the Office to suggest that characterization of a promoter is a lengthy process, illustrates the routine nature of characterizing even non-commercially available promoters. *Goswami* makes use of standard techniques to create and compare deletions of two promoters and identify the effect of the deletion. For example, Goswami at pages 45-46 mentions in the "Materials and Methods" section that a PCR-based method was used to construct progressive promoter deletions, and that two different cell types were then transiently transfected. If the techniques used to produce the promoter constructs and analyze their effects were unknown or unpredictable, it is unlikely this peer-reviewed journal would have permitted the authors to provide such a brief description of their methodology. As the Office Action notes, citing *In re Wands*, what is key is not whether some experimentation may be required, but whether the experimentation is undue. *Id.* at 5. Further, the Examples on pages 25-43 of the specification make use of several different art-recognized promoters for insect and mammalian expression systems to provide cap-dependent expression of the 5' cistron when demonstrating that the *lab* IRES element of SEQ ID NO. 1, its homolog

SEQ ID NO. 2, and fragments of SEQ ID NO. 1 can each be inserted into a bicistronic vector to drive cap-independent expression of the other cistron.

Promoters to provide the cap-dependent expression of the 5' cistron were not only known in the art, but were even commercially available as part of expression vector constructs. This public information more than adequately provides the skilled artisan with the guidance necessary to select the appropriate promoters and use them in the claimed vectors, particularly when combined with Applicants' disclosure. The M.P.E.P. states that "[a]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." M.P.E.P. §2164.01(b) (citing *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)). Although the promoter used in the nucleic acid vector for the expression of at least two cistrons necessarily varies depending upon the expression system chosen, so that the scope of the claims encompasses many different promoters, the selection of promoters appropriate to the different expression systems is a matter of routine practice in the art of molecular biology. In this respect a promoter in an expression vector is equivalent to, for example, an engine in a vehicle: many different engines would function in a given vehicle design, and the ordinary artisan would readily recognize that some engines are inappropriate for use in a specific vehicle. Similarly, many different promoters can function to drive cap-dependent expression of a cistron, and which promoters are appropriate for use in which expression vectors is readily apparent to the ordinary artisan in the field of molecular biology. Working examples showing inclusion of the IRES element in different expression systems comprising promoters, as provided in the

specification, therefore enable a broad scope of promoters within those expression systems. Further, Applicants note that a claim is fully enabled even if it encompasses within its scope some inoperative embodiments, so long as the experimentation involved in identifying the operative embodiments is not undue. *See* M.P.E.P. § 2164.08(b).

Because specific promoters are not essential elements of the invention, new claims 40-53 do not recite a promoter. These claims are directed to embodiments of the invention that are described and enabled in the specification, but that do not require recitation of a promoter to particularly point out and distinctly claim the inventive subject matter.

The Office has failed to meet its burden to provide a reasonable basis for questioning the enablement provided for the claimed invention. *See* M.P.E.P. § 2164.04. Applicants respectfully submit that when all factors are considered, the experimentation required to practice the claimed invention is not undue. The rejection of claims 1-11, 17 and 18 should therefore be withdrawn.

C. "Homolog"

The Office rejects claims 6, 18, 23-27, 29-31, and 33-35 under 35 U.S.C. § 112, first paragraph, as not being fully enabled because, according to the Office, the claims broadly encompass any homolog of SEQ ID NO. 1 but "neither the art nor the specification teaches what characteristics a 5' untranslated region (UTR) would have to predictably function as an internal ribosome entry site (IRES)." Office Action, page 7. The crux of the Office's position is that identification of each IRES is empirical so that

"all other homologs' 5'-UTR would need to be tested for IRES activity." *Id.* at 8. We respectfully disagree with the Office's position.

As an initial matter, claims 6, 18, 29-31 and 33-35 have been canceled and claim 23 amended. None of the pending claims specifically recite a "homolog." Although claim 24 recites "homologous recombination," homologous recombination refers to a mechanism for incorporating the genetic material of the transfer vector into the recombinant baculovirus, not a recitation of a homolog of SEQ ID NO. 1. Because new claim 53 does encompass within its breadth homologs of SEQ ID NO. 1 and SEQ ID NO. 2, the rejection of record will be addressed as applied to the newly added claim.

The specification provides working examples of various promoters used in insect and mammalian expression systems to provide cap-dependent expression of the 5' cistron and shows that the *lab* IRES element of SEQ ID NO. 1 can be inserted to drive cap-independent expression of the other cistron. This data is summarized in Table 1 on page 34 of the specification. The specification also shows in Example 6 on pages 34-36 that SEQ ID NO. 2, the human homolog IRES element in the 5'UTR of Homeobox A1, provides IRES activity in a mammalian expression system. The specification on pages 13-16 discloses that "a homolog of the *lab* IRES may have a primary or secondary structure similar to the *lab* IRES, and/or have IRES activity. Methods of detecting IRES activity are also disclosed, for example on page 16 and in the working examples.

The Office does not specifically address any of the factors necessary to show that it would require undue experimentation to practice the claimed invention before concluding that the specification does not enable the full scope of the claims. The

Office asserts without support that the art teaches that identification of an IRES is done empirically. Office Action, page 7. Even if this is so, the Office fails to show why an approach that the Office asserts is taught in the art would require undue experimentation. The Office also discounts Applicants' identification of the human homolog of SEQ ID NO. 1 as failing to provide any evidence of predictability. *See id.* at 8. But this reasoning would illogically suggest that if an Applicant verifies the expected function of a homolog, then the function of the homolog must have been unpredictable. Such a standard disregards the probative value of working examples in the specification, one of the factors that the Wands analysis specifically requires must be considered. The Office has failed to meet its burden to provide a reasonable basis for questioning the enablement provided for the claimed invention.

The rejection of record, even had it provided a reasonable basis for questioning the scope of enablement of the claims, does not apply to newly added claim 53. Although this claim also encompasses homologs of SEQ ID NO. 1, claim 53 both requires specific sequences (those with 80% or 90% sequence identity to SEQ ID NO. 1 or SEQ ID NO. 2, which are small nucleotide sequences of 239 or 244 nucleotides, respectively) and specific function (IRES activity.) The specification on pages 14-16 provides methods of both producing the sequences within the scope of claim 53, and of characterizing these sequences for IRES activity. This guidance, combined with the presence of working examples as described *supra* and the high level of skill in the art, enables the skilled artisan to make and use the full scope of claim 53 without undue experimentation.

D. **"Variant" or "Fragment"**

The Office also rejects claims 1-11, 17, 18, 20-22, 24, and 25 under 35 U.S.C. § 112, first paragraph, because the Office alleges the "specification does not teach how to make a variant or fragment of SEQ ID NO. 1 such that it functions as an IRES." Office Action, page 8. According to the Office, "variant" and "fragment" are each broad terms. *Id.* However, the Office in each case has to qualify the assertion that the specification does not teach how to make a "variant" or a "fragment" that has IRES activity with a phrase such as "beyond those disclosed in the specification." *Id.*

As discussed *supra* regarding the Office's rejection of claims reciting a "promoter" and "homolog," the Office fails to provide any reasonable basis for questioning the enablement provided for the claimed invention. Instead, the Office acknowledges, but then disregards, the working examples without any explanation for why the working examples do not, according to the Office, provide sufficient guidance such that the skilled artisan could make and use variants and fragments of SEQ ID NO. 1 that have IRES activity. The specification provides on pages 13-16 the methodology for making variants and fragments and then testing them for IRES activity. In addition, the specification provides in the Examples section several working examples creating variants and fragments of SEQ ID NO. 1 and characterizing these variants and fragments for IRES activity. Because the Office fails to provide any particular reasons why the guidance in this specification fails to enable the claimed invention, this rejection should also be withdrawn.

E. Host cells comprising vectors

According to the Office, claims 12-16 are rejected under 35 U.S.C. § 112, first paragraph, because the claims are broadly drawn to any host cell, but "claim 12 does not enable one skilled in the art to make or use any host comprising a nucleic acid vector of claim 1; claim 15 does not enable one skilled in the art to make or use any host cell comprising a nucleic acid vector of claim 6." Office Action, page 9. The Office notes that the actin 5C promoter does not work in mammalian cells and the CMV promoter does not work in Drosophila cells. *Id.*

Inoperative embodiments within the scope of a claim do not necessarily render the claim nonenabled. *See* M.P.E.P. § 2164.08(b). Instead, the question is whether a person skilled in the relevant art "could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art." *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984). As already discussed in detail *supra*, the selection of promoters appropriate to the different expression systems is a matter of routine practice in the art of molecular biology. Thus, those in the art would know that certain promoters are appropriate for mammalian cells while other promoters should be used in insect cells. Because the matter of selecting the appropriate promoter for the appropriate expression system, including the host cell, is routine, no undue experimentation would be required. Applicants respectfully request the Office withdraw this ground of rejection.

III. Rejection of claims 1-6, 8-27, 29-31, and 33-35 under 35 U.S.C. § 112,¶ 1, Written Description

Claims 1-6, 8-27, 29-31, and 33-35 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Office Action, page 9. According to the Office, the claims contain subject matter "which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the invention." *Id.* at 9-10.

A. "Promoter"

According to the Office, claims 1-19 are not adequately described under 35 U.S.C. § 112, first paragraph. Office Action, page 11. The Office reiterates its position that the claims are not enabled for any promoter. *Id.* at 10-11. Apparently relying on, or at least incorporating, this enablement argument, the Office then alleges that "the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants effective filing date." *Id.* at 10. The Office concludes that only the promoters pAC, pCMV, pOpIE2, pCycB and pPolh meet the written description requirement. *Id.* at 12.

Applicants' traversal of the rejection alleging that the specification does not enable the broad scope of the claims for any promoter has been set forth in full *supra* at Section II.B. and is incorporated herein. The Office's position regarding the description of the promoter feature of the claimed invention both mischaracterizes the promoter as critical to the invention and disregards the fact that promoters *were* conventional in the art as of Applicants' effective filing date. As discussed *supra*, the specification

acknowledges on pages 19-20 that promoters were well known in the art and that the promoter is determined by the expression system chosen. The inventive feature of the vector does not involve the selection of any specific promoter of subsection (a). New claims 40-53 illustrate that recitation of a promoter is not required to particularly point out and distinctly claim the inventive subject matter. Information which is well known in the art need not be described in detail in the specification." M.P.E.P. § 2163.II.A.2 (citing *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 137980, 231 USPQ 81, 90 (Fed. Cir. 1986)).

Applicants respectfully submit that the skilled artisan would have readily appreciated that Applicant was in possession of the claimed invention as a whole at the time the application was filed. The rejection should therefore be withdrawn.

B. "Variants, fragments, and homologs"

The Office also alleges that variants, fragments, and homologs of SEQ ID NO. 1 are not adequately described in the specification so that claims 1-6, 8-18, 20-27, 29-31, and 33-35 therefore lack adequate written description under 35 U.S.C. § 112, first paragraph. Office Action, pages 10-11. The Office lists the working examples of IRESes and states that only these meet the written description requirement. *Id.* at 12. The Office points to the decision in *Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) ("*Lilly*"), in support of its position. *Id.* at 12-13.

In *Lilly*, the court concluded that a claim to a genus of cDNAs encoding mammalian insulin were not adequately described by the disclosure of a single nucleotide sequence encoding rat insulin. *Lilly* at 1569. However, the court noted that

"[a] description of a genus of cDNAs may be achieved by means of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus." *Id.* In addition, the court indicated that adequate written description could also be provided by "a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." *Id.*

Unlike the situation in *Lilly*, Applicants describe several species falling within the scope of the genus of "variants, fragments, and homologs" of SEQ ID NO. 1 that have IRES function. For example, Table 2 on page 37 of the specification summarizes three sequences that are fragments of SEQ ID NO. 1. The relative level of activity of these fragments is shown in Figure 6A. One variant sequence in which the nucleotides at positions 124-127 were substituted with other nucleotides is also described in Table 2 and Figure 6A, as are two variants of SEQ ID NO. 1 in which part of the internal sequence was deleted. SEQ ID NO. 2, the human homolog of SEQ ID NO. 1, is described by providing its nucleotide sequence. In addition, a variant of SEQ ID NO. 2 is described containing nucleotide substitutions. See page 38 of the specification and Figure B. Thus Applicants have provided multiple species within the claimed genus of sequences related to SEQ ID NO. 1 (i.e., variants, fragments, and homologs of SEQ ID NO. 1) which have IRES activity. This description of multiple species within the claimed genus clearly distinguishes the instant case from the factual situation in *Lilly.*

Further, the claims couple the structural requirement of relatedness to SEQ ID NO. 1, which is a relatively small sequence of 239 nucleotides, with the testable function of IRES activity. The *Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, "Written Description" Requirement*, 66 Fed. Reg. 1099 (2001) indicate

that for claims drawn to a genus, the written description requirement may be satisfied by either "sufficient description of a representative number of species by actual reduction to practice" or "by disclosure of . . . functional characteristics coupled with a known or disclosed correlation between function and structure." *Id.* at 1106. The disclosure provides far more than the description of a single species upon which the claim to the genus is based. Finally, Applicants have canceled those claims reciting "homolog" and presented a new claim that encompasses homologs within its scope, but provides a clearer structural reference by inclusion of a SEQ ID NO. Applicants respectfully submit that the written description requirement for the currently claimed genus has been met and the rejection should be withdrawn.

IV. Conclusion

In view of the foregoing remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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